

**Remarks**

By the present amendments, previous claims 1-23 and 26 have been deleted and new claims 27-60 have been added. New claims 27 and 44 find support in previous claims 20 and 21, respectively. Support for parenteral administration of the preparation finds support in the disclosure for example on page 2, line 21 to page 3, line 11 and on page 4, lines 12-19. New claims 28-43 and 45-60 find support in previous claims 2-14, 16, 17 and 22. Applicant believes that such amendments do not contain new matter. The amendments to the claims have been made without prejudice and without acquiescing to any of the Examiner's objections. Applicant reserves the right to pursue any of the deleted subject matter in a further divisional, continuation or continuation-in-part application.

The office action dated December 5, 2001 has been carefully considered. It is believed that the amended claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

**35 USC §102**

The Examiner has objected to claims 1, 7, 9-12, 14-15, 18 and 20 under 35 USC §102(b) as being anticipated by Beggs et al. (WO 95/01155).

By the present amendment, the claims have been amended to recite a method of increasing the serum half-life of an immune globulin by parenterally administering an immune globulin preparation comprising an immune globulin and at least one non-ionic surface active agent. The claims directed to the immune globulin preparation *per se* have been deleted without prejudice. Beggs et al. does not disclose that surface active agents are useful in increasing the serum half life of an immune globulin. Beggs et al also does not teach or suggest that immune globulins in combination with a surface active agent can be administered parenterally. As a result, Beggs et al cannot be said to anticipate the claims currently of record.

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The Examiner has also objected to claims 1, 7, 14-15, 17-20 and 22 under 35 USC §102(b) as being anticipated by Hirao et al. (EP 278,422). We respectfully disagree with the Examiner for the reasons that follow.

As stated above, the claims have been amended in order to recite a method of increasing the serum half-life of an immune globulin by parenterally administering a preparation comprising immune globulin and at least one non-ionic surface active agent. Applicants maintain their position that Hirao et al does not teach an injectable composition comprising a non-ionic surfactant as sorbitol is a sugar alcohol molecule and is not a non-ionic surfactant.

The Examiner has cited page 6 lines 23-24 of the instant application, which states "(a) non-ionic surface active agent contains a neutral group such as a carbohydrate which can hydrogen bond with water." The Examiner further states that, based on the above statement, sorbitol is encompassed within the definition of a non-ionic surface active agent. Applicant submits that the above statement is a description of only the hydrophilic moiety of a non-ionic surface active agent, and not a definition of a complete non-ionic surface active agent. The Examiner's is kindly directed to page 6 lines 13-24 of the instant application that defines surfactants.

"Surface active agents (also termed surfactants) are compounds that can lower the surface tension of water. All surface active agents are **amphipathic** possessing a **hydrophobic end** (e.g. one or more hydrocarbon chains(s)) as well as a **hydrophilic moiety** (which may or may not be ionic). A surface active agent may be classified as anionic, cationic or non-ionic, depending on the nature of its hydrophilic moiety. Soaps with carboxylate or sulphonate groups carry net negative charges and are examples of anionic surface active agents. Benzalkonium, an N-benzyl quaternary ammonium chloride and an antibacterial agent, carries a net positive charge and is an example of a cationic surface active agent. A non-ionic surface active agent contains a

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neutral group such as a carbohydrate which can hydrogen bond with water.”  
(Emphasis added)

Therefore, a surface active agent is an amphipathic molecule possessing a hydrophobic end and a hydrophilic end. In the case of Span™, the hydrophilic end is the sugar alcohol anhydrite, derived from sorbitol, and the hydrophobic end is the partial esters of common fatty acids that are attached to sorbitol (page 6 lines 25-31). Specific examples of such long chain fatty acids linked to sorbitan to generate the amphipathic molecule are provided on page 6 line 31 to page 7 line 2.

As mentioned above, Hirao et al teaches a composition comprising sorbitol and an immune globulin. Applicant maintains that sorbitol is not a surface active agent as sorbitol is not an amphipathic molecule since it does not contain a hydrophobic end. Further, Hirao does not disclose that surface active agents are useful in increasing the serum half life of an immune globulin. As a result, Hirao et al can not be said to anticipate the claims as amended herewith.

In view of the foregoing, we respectfully request that the objections to the claims as being anticipated by Beggs et al. and Hirao et al. be withdrawn.

### **35 USC §103**

The Examiner has rejected claims 2-4, 8, 15-17, 19-20, 22 and 26 under 35 USC §103(a) as being obvious over Beggs et al. in view of Friesen. We respectfully disagree with the Examiner for the reasons that follow.

As mentioned above, the claims of the present application have been amended in order to recite a method of increasing serum half-life of an immune globulin comprising parenterally administering an immune globulin and at least one non-ionic surface active agent. None of the references cited by the Examiner teach or remotely suggest that a non-ionic surface active agent is useful in increasing the serum half-life of an immune globulin. Applicant contends that the oral care compositions taught

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by Beggs, are not in the same field as compositions for parenteral administration. There is no motivation to a person of ordinary skill in the art of preparing immune globulin compositions for parenteral administration to search in the field of oral care products for substances that may stabilize immune globulins in serum. Further, the oral care products taught by Beggs et al are completely unsuitable for parenteral administration and would in no way lead one of skill in the art to the present invention.

First, the oral care product taught by Beggs et al cannot be administered parenterally. Beggs et al teaches oral compositions for "the care of the human teeth and mouth ... such as dentifrices, toothpastes, gels, mouthwashes, powders, tablets, lozenges, gargle solutions and the like." page 1, lines 14-17. Applicant submits that the oral compositions cited by Beggs et al are not suitable for parenteral injection as not one of these compositions is a physiologically compatible medium. Immune globulin compositions for parenteral administration are very different from oral care compositions taught by Beggs et al. Specific features of immune globulin compositions for parenteral administration are taught in the instant application: a) preparation of the immune globulin for parenteral administration (page 16 line 3 to page 18 line 17); b) the non-ionic surface active agents that are safe for parenteral administration and that prolong the serum half-life of an immune globulin (page 18 line 18 to page 19 line 14); c) formulation of the immune globulin for parenteral administration (page 19 line 15 to page 21 line 3); and d) the therapeutic dose of immune globulin for parenteral administration (page 21 line 4-23). Applicant has reviewed the specification of Beggs et al, and Applicant contends that Beggs et al does not teach any one of these points. As such, Applicant contends that Beggs et al does not teach how to formulate an immune globulin composition suitable for parenteral administration.

Furthermore, Beggs et al does not teach administration of an immune globulin wherein the immune globulin is directed to the blood stream, or that non-ionic surfactants stabilize the immune globulin in the blood stream. The Examiner has stated that Beggs et al teaches a class of non-ionic surfactants that combine good

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compatibility with antibodies, providing improved immunoreactivity and enhancing antibody binding. Applicant respectfully submits that Beggs et al teaches non-ionic surfactants combines good compatibility with antibodies in oral care products, improved immunoreactivity and enhanced antibody binding in an oral environment. Applicant contends that the antibodies in the oral composition of Beggs et al bind antigens within the oral cavity. Such antibodies do not enter and circulate within the blood stream of the person using the oral compositions. As such, there is no teaching in Beggs et al that non-ionic surfactants will prolong the half-life of an immune globulin in the blood stream, as taught in the instant application.

Applicant submits that Beggs et al teaches oral care compositions. Beggs et al does not teach how to formulate an immune globulin composition that may be administered in a parenteral manner. Furthermore, Beggs et al does not teach that his antibodies enter the blood stream, and does not teach that non-ionic surfactants will increase the serum half-life of immune globulins. Therefore Beggs et al does not teach or suggest an immune globulin composition for parenteral administration as claimed in the amended claims of in the instant application.

The deficiencies in Beggs et al are not remedied by Friesen. Friesen teaches anti-Rh<sub>0</sub>D immune globulin that can be administered intravenously for use in the prevention of isoimmunization of Rh-negative woman pregnant with Rh-positive children (Friesen, page 1 lines 18-21). As the Rh<sub>0</sub>D antigen is found on red blood cells, the anti-Rh<sub>0</sub>D immune globulin, taught by Friesen, must be parenterally administered to reach the red blood cells. Beggs teaches an oral care composition containing antibodies that cannot enter the blood stream. As such, there is no motivation in Friesen to combine a parenteral immune globulin composition with an oral care product. Friesen provides no suggestion to a person skilled in the art that the addition of a surface active agent could prolong the serum half-life of the immune globulin, or that prolonging the serum half-life of immune globulins is required.

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There is no motivation for a person of ordinary skill in the art of preparing immune globulin compositions for parenteral administration to search the field of oral care products. Further, as stated above, Beggs et al provides no motivation to prepare a parenteral solution containing an immune globulin and a surface active agent. At best, Beggs et al teaches that non-ionic surface active agents may stabilize the immune globulin compositions to increase the shelf life of oral care compositions. Beggs et al provides no teaching, guidance or suggestion that the non-ionic surfactants would have any effect on the half-life of antibodies *in vivo* in serum. Therefore, there would be no motivation for one having read Friesen to look to Beggs et al. for methods of prolonging the half life of the immune globulin in the serum.

The Examiner has also objected to claims 5-7 under 35 USC §103(a) as being unpatentable over Beggs et al. in view of Moore et al. We respectfully disagree with the Examiner for the reasons that follow.

Our comments on Beggs et al appear above. The deficiencies in Beggs et al are not remedied by Moore et al. Moore et al. merely teach that anti-c immune globulin is known to be found in human sera. Moore et al provide no teaching as to the preparation of an anti-c immune globulin, and no teaching that stabilization of such immune globulin is required. Moore et al. provide no teaching or suggestion that the addition of non-ionic surface active agents could increase the serum half-life of anti-c immune globulin.

The Examiner has further objected former claim 13 (analogous to new claim 39) for being unpatentable over Beggs et al. in view of Jansen et al. (EP 318,081). We respectfully disagree with the Examiner for the reasons that follow.

Our comments on Beggs appear above. The deficiencies in Beggs et al are not remedied by Jansen et al. Applicant submits that former claim 13 is directed to two non-ionic surfactants selected from the group of polyethylene sorbitan fatty acid esters listed in new claim 39. Jansen et al. teaches the stabilization of antibodies in

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aqueous solutions with a combination of polyoxpropylene-polyethylene block polymer (POP-POE block polymer) and a phospholipid. The POP-POE block polymer, taught by Jansen, consists of alternating stretches of polyoxpropylene (POP) residues and polyethylene (POE) residues. Of the polyethylene sorbitan fatty acid esters listed in new claim 39, not one is a POP-POE block polymer. Furthermore, the phosphate groups of phospholipids are negatively charged, and are therefore anionic surfactants, as defined on page 6 lines 13-16 of the instant application. Therefore, Applicant submits that Jansen does not teach the invention of new claim 39 as POP-POE block polymers are not listed in new claim 39, and phospholipids are anionic surfactants. Finally, there is no teaching or suggestion in Jansen that non-ionic surfactants could be used to increase the serum half-life of immune globulin preparations.

In view of the foregoing, we respectfully request that all of the objections to the claims under 35 USC §103 be withdrawn.

**35 USC §112, second paragraph**

The Examiner has objected to claims 1-23 and 26 under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Examiner comments that the claims are indefinite because the immune globulin lacks any defining characteristics. We respectfully disagree with the Examiner for the reasons that follow.

The Examiner states that the claims do not provide any structural criteria such as molecular weight, deposit information or sequence information about the immune globulin. We respectfully point out to the Examiner that the claims are not meant to be limited to a specific immune globulin that binds a specific epitope. Applicant submits that the term "immune globulin", as defined in the instant application, refers to a broad range of antibodies that includes, but is not limited to, various classes and subclasses of antibodies, combinations of antibodies to different epitopes, various

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fragments of antibodies, monoclonal antibodies, and other antibodies. The Examiner is directed to page 15 lines 11-17 of the instant application which states: "The immune globulin of the present invention can be any immune globulin including IgG (all subtypes), IgA, IgD, IgE and IgM and includes fragments of the immune globulins such as Fab' and F(ab')<sub>2</sub> fragments." The Examiner is further directed to page 15 lines 18-26, which states: "An example of immune globulin that can be used in the present invention is Rh immune globulin or Rh antibodies. ... The Rh antibodies of the present invention may be preparations from plasma enriched for Rh antibodies, polyclonal antibodies, monoclonal antibodies, antibody fragments (e.g. Fab and F(ab')<sub>2</sub>), and those produced by recombinant DNA technology." In one example, an immune globulin is prepared by the isolation of immune globulins from mammalian serum (page 2, lines 12-13). Such an immune globulin preparation will result in a mixture of antibodies that will recognize various epitopes. The Examiner is directed to page 1 line 27 to page 5 line 2, page 15 lines 18-30, and page 16 line 3 to page 18 line 17 of the instant application. Such pages describe other examples of immune globulins that may be used in the present invention, various methods of preparing such immune globulins, and several commercially available immune globulin preparations. Applicant submits that the term "immune globulin" is defined in the instant specification, and that the definition does not lend itself to be limited to having a specific sequence or binding to a specific epitope.

In view of the foregoing, we respectfully request that all of the objections to the claims under 35 USC §112, second paragraph, be withdrawn.

### **35 USC §101**

The Examiner has objected to claims 18-19 under 35 USC §101. These claims have been deleted by the present amendment which overcomes this objection.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

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Should the Examiner deem it beneficial to discuss the application in greater detail, he is kindly requested to contact the undersigned by telephone at (416) 364-7311 at his convenience.

Respectfully submitted,

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**Version with markings to show changes made****In the Claims:**

Claims 1-23 and 26 currently of record have been deleted.

New claims 27-60 have been added as follows:

27. (New) A method of increasing the serum half-life of an immune globulin comprising parenterally administering an immune globulin preparation comprising an immune globulin and at least one non-ionic surface active agent, said one or more non-ionic surface active agent(s) in a concentration sufficient to increase the serum half-life of the immune globulin to an animal in need thereof.

28. (New) A method according to claim 27 wherein the immune globulin is anti-Rh<sub>0</sub>D immune globulin.

29. (New) A method according to claim 27 wherein the anti-Rh<sub>0</sub>D immune globulin has an IgG purity of greater than about 95% and a monomeric protein content of greater than about 94%.

30. (New) A method according to claim 29 which is aqueous.

31. (New) A method according to claim 27 wherein the immune globulin is anti-c immune globulin.

32. (New) A method according to claim 31 wherein the anti-c immune globulin has an IgG purity of greater than about 95% and a monomeric protein content of greater than about 94%.

33. (New) A method according to claim 32 which is aqueous.

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34. (New) A method according to claim 27 wherein the concentration of the immune globulin is about 2 weight percent to about 10 weight percent.

35. (New) A method according to claim 27 wherein the one or more non-ionic surface active agent(s) is(are) a sorbitan ester of a fatty acid.

36. (New) A method according to claim 35 wherein the non-ionic surface active agent(s) is(are) selected from the group consisting of sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, and sorbitan trioleate.

37. (New) A method according to claim 27 wherein the one or more non-ionic surface active agent(s) is(are) a polyoxyethylene sorbitan ester of a fatty acid.

38. (New) A method according to claim 37 wherein the non-ionic surface active agent(s) is(are) selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (4) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (4) sorbitan monostearate, polyoxyethylene (20) sorbitan tristearate, polyoxyethylene (20) sorbitan monooleate, polyoxyethylene (5) sorbitan monooleate, and polyoxyethylene (20) sorbitan trioleate.

39. (New) A method according to claim 27 wherein two or more non-ionic surface active agents are selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (4) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (4) sorbitan monostearate, polyoxyethylene (20) sorbitan tristearate, polyoxyethylene (20) sorbitan monooleate, polyoxyethylene (5) sorbitan monooleate, and polyoxyethylene (20) sorbitan trioleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, and sorbitan trioleate.

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40. (New) A method according to claim 27 wherein the concentration of the one or more non-ionic surface active agent(s) is(are) about 0.01 weight percent to about 0.5 weight percent.

41. (New) A method according to claim 27 wherein the immune globulin preparation is a lyophilized preparation.

42. (New) A method according to claim 27 wherein the immune globulin preparation comprises:

about 3-8% human anti-Rh<sub>0</sub>D immune globulin with an IgG purity of greater than 95% and a monomeric protein content of greater than 94%;

sodium chloride at about 0.25% (w/v);

very low level buffer with essentially no ionic strength;

Polysorbate 80<sup>®</sup> at about 0.01% to about 0.5% (w/v); and

L-glycine at about 0.1M.

43. (New) A method according to claim 27 wherein the one or more non-ionic surface agents are selected from the group consisting of glyceryl monooleate; and a polyvinyl alcohol.

44. (New) A method of reducing the elevation of neutrophil counts in a recipient of immune globulin comprising parenterally administering an immune globulin preparation comprising an immune globulin and at least one non-ionic surface active agent, said one or more non-ionic surface active agent(s) in a concentration sufficient to increase the serum half-life of the immune globulin to an animal in need thereof.

45. (New) A method according to claim 44 wherein the immune globulin is anti-Rh<sub>0</sub>D immune globulin.

46. (New) A method according to claim 44 wherein the anti-Rh<sub>0</sub>D immune globulin has an IgG purity of greater than about 95% and a monomeric protein content of greater than about 94%.
47. (New) A method according to claim 46 which is aqueous.
48. (New) A method according to claim 44 wherein the immune globulin is anti-c immune globulin.
49. (New) A method according to claim 48 wherein the anti-c immune globulin has an IgG purity of greater than about 95% and a monomeric protein content of greater than about 94%.
50. (New) A method according to claim 49 which is aqueous.
51. (New) A method according to claim 44 wherein the concentration of the immune globulin is about 2 weight percent to about 10 weight percent.
52. (New) A method according to claim 44 wherein the one or more non-ionic surface active agent(s) is(are) a sorbitan ester of a fatty acid.
53. (New) A method according to claim 52 wherein the non-ionic surface active agent(s) is(are) selected from the group consisting of sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, and sorbitan trioleate.
54. (New) A method according to claim 44 wherein the one or more non-ionic surface active agent(s) is(are) a polyoxyethylene sorbitan ester of a fatty acid.
55. (New) A method according to claim 54 wherein the non-ionic surface active agent(s) is(are) selected from the group consisting of polyoxyethylene (20) sorbitan

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monolaurate, polyoxyethylene (4) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (4) sorbitan monostearate, polyoxyethylene (20) sorbitan tristearate, polyoxyethylene (20) sorbitan monooleate, polyoxyethylene (5) sorbitan monooleate, and polyoxyethylene (20) sorbitan trioleate.

56. (New) A method according to claim 44 wherein two or more non-ionic surface active agents are selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (4) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate; polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (4) sorbitan monostearate, polyoxyethylene (20) sorbitan tristearate, polyoxyethylene (20) sorbitan monooleate, polyoxyethylene (5) sorbitan monooleate, and polyoxyethylene (20) sorbitan trioleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, and sorbitan trioleate.

57. (New) A method according to claim 44 wherein the concentration of the one or more non-ionic surface active agent(s) is(are) about 0.01 weight percent to about 0.5 weight percent.

58. (New) A method according to claim 44 wherein the immune globulin preparation is administered intravenously.

59. (New) A method according to claim 44 wherein the immune globulin preparation comprises:

about 3-8% human anti-Rh<sub>0</sub>D immune globulin with an IgG purity of greater than 95% and a monomeric protein content of greater than 94%;

sodium chloride at about 0.25% (w/v);

very low level buffer with essentially no ionic strength;

Polysorbate 80™ at about 0.01% to about 0.5% (w/v); and

L-glycine at about 0.1M.

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60. (New) A method according to claim 44 wherein the one or more non-ionic surface agents are selected from the group consisting of glyceryl monooleate; and a polyvinyl alcohol.